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Cancer Res 1998 Jul 15;58(14):3078-86

Human renal cell carcinoma antigen-specific CTLs: antigen-driven selection and long-term persistence in vivo.

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Renal cell carcinomas (RCCs) are thought to be immunogenic, because cytokine-induced and even spontaneous tumor regression has been observed in a significant number of patients. However, little is known about the nature of immune responses that might lead to tumor regression. We studied naturally arising human T-cell responses against RCC by combining molecular analyses of T-cell receptor (TCR) usage in primary tumors in situ with functional analyses of tumor-infiltrating lymphocytes (TILs) in vitro. TILs of patient 26 that were cultured in vitro showed a human leukocyte antigen (HLA-A*0201)-restricted cytotoxic activity specific for autologous tumor cells. These tumor-derived lymphocytes were dominated by a family of T cells expressing V alpha20- and V beta22-positive TCRs. Their specificity-conferring third complementarity-determining regions were highly homologous with respect to the loop length and selection of particular amino acids in both TCR chains. These characteristics are similar to those reported for antigen-selected murine T cells recognizing immunodominant epitopes of non-self proteins. To evaluate the biological significance of these CTLs in vivo, we analyzed the corresponding TCR transcripts in the cryopreserved tumor material of patient 26 and in a second HLA-A*0201-positive RCC patient whose tumor cells were also lysed by TIL-26. The in situ TIL populations of both patients used related families of highly homologous TCRs, supporting the contention that immunodominant responses directed against a shared tumor-associated antigen occurred in both individuals in vivo. Furthermore, in the absence of overt metastatic disease, the tumor antigen-specific CTLs of patient 26 were shown to persist in the periphery 4 years after removal of the primary tumor. These results demonstrate that antigen-driven T-cell responses specific for spontaneously arising carcinomas developed in these patients and showed long-term persistence, even in the absence of immunotherapy.

PMID: 9679974, UI: 98343568